Complete Summary

GUIDELINE TITLE

(1) Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. (2) 2007 addendum.

BIBLIOGRAPHIC SOURCE(S)

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Bethesda (MD): Department of Health and Human Services (DHHS); 2006 Oct 10. 116 p. [340 references]

Panel on Antiretroviral Guidelines for Adults and Adolescents. Supplement to the guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents - October 10, 2006. Bethesda (MD): Department of Health and Human Services (DHHS); 2007 Apr 30. 1 p. [2 references]

GUIDELINE STATUS

This is the current release of the guideline. It was last updated on October 10, 2006; an addendum was released April 30, 2007.

These guidelines generally represent the state of knowledge regarding the use of antiretroviral agents. However, as the science rapidly evolves, the availability of new agents and new clinical data may rapidly change therapeutic options and preferences. The guidelines are therefore updated frequently by the Panel, which meets monthly by teleconferencing to make ongoing revisions as necessary. All revisions are summarized and highlighted on the AIDSinfo Web site. Proposed revisions are posted for a public comment period, generally for 2 weeks, after which comments are reviewed by the Panel prior to finalization. Comments can be sent to aidsinfowebmaster@aidsinfo.nih.gov.

Status information regarding this guideline is available from the AIDSinfo Web site, telephone (800) 448-0440, fax (301) 519-6616; TTY (888) 480-3739.

* * REGULATORY ALERT * *

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- September 10, 2007, Viracept (nelfinavir mesylate): Pfizer issued a Dear Healthcare Professional Letter to inform healthcare professionals of the presence of ethyl methanesulfonate (EMS), a process-related impurity in Viracept and to provide guidance on the use of Viracept in pregnant women and pediatric patients.
- August 16, 2007, Baraclude (Entecavir): Revisions to the prescribing information for Baraclude to indicate that the drug is not recommended for HIV/hepatitis B virus (HBV) co-infected patients who are not also receiving highly active antiretroviral therapy (HAART) due to the potential for the development of HIV resistance.
- June 30, 2006, Aptivus (tipranavir): Healthcare professionals informed of important new safety information that includes an addition to the drug's Black Box Warning regarding reports of both fatal and non-fatal intracranial hemorrhage.
- June 15, 2005, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): U.S. Food and Drug Administration (FDA) recommended proposed labeling for both the prescription and over the counter (OTC) NSAIDs and a medication guide for the entire class of prescription products.
- April 7, 2005, Non-steroidal anti-inflammatory drugs (NSAIDS) (prescription and OTC, including ibuprofen and naproxen): FDA asked manufacturers of prescription and non-prescription (OTC) non-steroidal anti-inflammatory drugs (NSAIDs) to revise their labeling to include more specific information about potential gastrointestinal (GI) and cardiovascular (CV) risks.
- January 19, 2005, Nevirapine (viramune): Labeling has been revised to include more information on liver toxicity associated with long term use, including a Medication Guide informing patients about risks when used for the treatment of human immunodeficiency virus (HIV).

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Human immunodeficiency virus (HIV) infections (including asymptomatic, established, and acute HIV)
- Acquired immunodeficiency syndrome (AIDS)

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Pediatrics
Preventive Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To update the May 2006 guidelines
- To use the advances in current understanding of the pathogenesis of human immunodeficiency virus (HIV) in the infected person to translate scientific principles and data obtained from clinical experience into recommendations that can be used by the clinician and patient to make therapeutic decisions

TARGET POPULATION

Adults and adolescents infected with human immunodeficiency virus (HIV)

These guidelines focus on treatment for adults and adolescents. Separate guidelines outline how to use antiretroviral therapy for such populations as pregnant women, pediatric patients, and health care workers with possible occupational exposure to HIV. There is a brief discussion of the management of women in reproductive age and pregnant women in this document. However, for more detailed and up-to-date discussion on this and other special populations, the Panel defers to the designated expertise outlined by panels that have developed these guidelines.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Basic evaluation
    - Pre-treatment evaluation
        - Medical history, physical examination
        - Laboratory tests, including human immunodeficiency virus antibody, CD4 cell count, plasma HIV ribonucleic acid (RNA), and other tests, as indicated
    - Initial assessment and monitoring for therapeutic response
        - CD4 counts
        - Viral load

2. Drug resistance testing
3. Initial regimens for the antiretroviral-naïve patient
    - Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen (1 NNRTI + 2 nucleoside reverse transcriptase inhibitors [NRTI])
    - Protease inhibitor (PI)-based regimen (1-2 PI + 2 NRTI)
        - Alternative PI-based regimen
    - Dual nucleoside option as part of initial combination therapy

4. Managing treatment-experienced patients
    - Assessment of treatment failure
    - Changing antiretroviral therapy
    - Therapeutic drug monitoring
    - Discontinuation or interruption of antiretroviral therapy
5. Considerations for antiretroviral use in special populations
    - Acute HIV infection
    - HIV-infected adolescents
    - Injection drug users
    - HIV-infected women of reproductive age and pregnant women
    - Patients with co-infections (hepatitis B, Hepatitis C, Mycobacterium tuberculosis)
6. Prevention counseling

MAJOR OUTCOMES CONSIDERED

- Viral load
- Immunologic function
- Adherence to treatment
- Therapy-associated adverse effects
- Quality of life
- Human immunodeficiency virus (HIV)-related morbidity and mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Data Used for Making Recommendations

In its deliberations for the guidelines, the Panel on Clinical Practices for Treatment of HIV Infection reviewed clinical trial data published in peer-reviewed journals and data prepared by manufacturers for U.S. Food and Drug Administration (FDA) review. In selected cases, data presented in abstract format in major scientific meetings were also reviewed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Categories reflecting the quality of evidence supporting the recommendations:

I. At least one randomized trial with clinical results
II. Clinical trials with laboratory results
III. Expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendation

A. Strong
B. Moderate
C. Optional
D. Should usually not be offered
E. Should never be offered

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

All revisions are summarized and highlighted on the AIDSinfo Web site. Proposed revisions are posted for a public comment period, generally for 2 weeks, after which comments are reviewed by the guideline panel prior to finalization.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendations usually are followed by levels of evidence (I-III) identifying the type of supporting evidence and strength of recommendation grades (A-E). Definitions for these are presented at the end of the "Major Recommendations" field.

2007 Addendum

Note from the National Guideline Clearinghouse (NGC) and the Department of Health and Human Services (DHHS): On April 30, 2007, the DHHS released an addendum to these guidelines on the use of entecavir in hepatitis B virus (HBV)/human immunodeficiency virus (HIV) co-infected patients. The new recommendation is provided below and is repeated under the heading "2007 Addendum" wherever the 2006 guidelines made a recommendation for the use of entecavir for HBV/HIV co-infected patients.

Previously, the guidelines recommended entecavir as an option for patients who required treatment for Hepatitis B virus (HBV) but not HIV infection. This recommendation was based on in vitro data showing no significant activity of entecavir against HIV-1. A recent case series of three patients who received entecavir without concomitant antiretroviral therapy reported a 1 $\log_{10}$ decline in HIV-RNA levels and emergence of M184V mutations in one patient who was studied in detail.

Based on these preliminary findings, the Panel recommends that:

For HBV/HIV co-infected patients, entecavir should not be used for the treatment of HBV infection without concomitant treatment for HIV.

October 10, 2006 Guidelines

Note from the National Guideline Clearinghouse (NGC) and the Department of Health and Human Services: These guidelines were updated by the developer on October 10, 2006. Following are the major changes that have been made to the May 4, 2006, version of the guidelines, followed by the guideline recommendations. Please refer to the original guideline document at the AIDSinfo Web site for further details.

What's New in the Document?

The following changes have been made to the May 4, 2006, version of the guidelines:

What to Start Recommendations

- The Panel confirms that the regimens with the most experience in demonstrating virologic and immunologic efficacy are those composed of 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) + 2 nucleoside reverse transcriptase inhibitors (NRTI) or of a protease inhibitor (PI) (with or without ritonavir boosting) + 2 NRTI. The Panel also confirms that selection of an antiretroviral regimen should be individualized based on patient- and drug-specific factors.
- The Panel revised its recommendations for preferred and alternative antiretroviral components based on reported results from several randomized trials in treatment-naïve patients and on safety data that have emerged since the last revision. Specific recommendations can be found in Tables 6a and 6b in the original guideline document. Rationale for the recommendations is outlined in the text.
- The revised recommendations for antiretroviral-naïve patients are summarized below. Clinicians are recommended to construct a regimen by choosing one component from Column A + one component from Column B.

	Column A		Column B
	NNRTI	PI	2-NRTI
Preferred (alphabetical order)	Efavirenz (AI I)	Atazanavir + ritonavir (AI I I) Fosamprenavir + ritonavir twice daily (BID) (AI I) Lopinavir/ritonavir BID (AI I)	Tenofovir/emtricitabine (AI I) Zidovudine/lamivudine (AI I)
Alternative (alphabetical order)	Nevirapine (BI I)	Atazanavir (unboosted) (BI I) Fosamprenavir (unboosted) (BI I) Fosamprenavir + ritonavir once daily (BI I) Lopinavir/ritonavir once daily (BI I)	Abacavir/lamivudine (BI I) Didanosine + lamivudine (BI I)

- Several options are considered acceptable as initial components but, in the view of the Panel, are inferior to the preferred or alternative components; however, they may be preferred in selected settings. These options include nelfinavir, ritonavir-boosted saquinavir, stavudine + lamivudine, and a triple-NRTI regimen containing abacavir + zidovudine + lamivudine.

The Following Tables Have Been Updated:

- Table 6 has been revised and divided into Tables 6a and 6b to reflect the above revisions.

- Tables 7 and 9 have been updated to reflect changes in the recommendations.
- Table 10 has been updated with results from several recently published clinical trials.
- Tables 11 to 13, 15, and 17 to 19 have been updated to include information regarding darunavir and the fixed-dose combination of efavirenz/emtricitabine/tenofovir (Atripla™) and new safety information and black box warnings regarding rare cases of intracranial hemorrhages occurring in patients receiving tipranavir.
- Tables 20 to 22b have been updated to include darunavir drug-drug interactions.
- Tables 28 and 29 have been revised according to updates in the Perinatal Guidelines to incorporate preclinical and clinical data relevant to the use of darunavir during pregnancy and new recommendations on antiretroviral use during pregnancy.
- Table 30 has been updated to include information on expanded access programs for two investigational agents, TMC125 and MK-0518.

Basic Evaluation

Pretreatment Evaluation

Each patient initially entering care should have a complete medical history, physical examination, and laboratory evaluation. The purpose is to confirm the presence of human immunodeficiency virus (HIV) infection, determine if HIV infection is acute, determine the presence of co-infections, and assess overall health condition as recommended by the primary care guidelines for the management of HIV-infected patients.

The following laboratory tests should be performed for each new patient during initial patient visits:

- HIV antibody testing (if laboratory confirmation not available) (AI)
- $CD4^+$ T-cell count (AI)
- Plasma HIV ribonucleic acid (RNA) (AI)
- Complete blood count, chemistry profile, transaminase levels, blood urea nitrogen (BUN) and creatinine, urinalysis, Rapid Plasma Reagin (RPR) or Venereal Disease Research Laboratory (VDRL) testing, tuberculin skin test (unless a history of prior tuberculosis or positive skin test), Toxoplasma gondii immunoglobulin G (IgG), Hepatitis A, B, and C serologies, and Pap smear in women (AIII)
- Fasting blood glucose and serum lipids if considered at risk for cardiovascular disease and for baseline evaluation prior to initiation of combination antiretroviral therapy (AIII); and
- For patients with pretreatment HIV RNA >1,000 copies/mL - genotypic resistance testing prior to initiation of therapy (BIII); if therapy is to be deferred, resistance testing may still be considered. (CIII) (See below under "Utilization of Drug Resistance Testing in Clinical Practice.")

In addition:

- An optional test for Chlamydia trachomatis and Neisseria gonorrhoeae in order to identify high risk behavior and the need for sexually transmitted disease (STD) therapy (BII); and
- Chest x-ray if clinically indicated (BIII)

Patients living with HIV infection must often cope with multiple social, psychiatric, and medical issues. Thus, the evaluation should also include assessment of substance abuse, economic factors, social support, mental illness, comorbidities, and other factors that are known to impair the ability to adhere to treatment and to alter outcomes. Once evaluated, these factors should be managed accordingly.

Initial Assessment and Monitoring for Therapeutic Response

$CD4^+$ T-Cell Count

Use of CD4+ T Cell Count for Initial Assessment

The $CD4^+$ count is usually the most important consideration in decisions to initiate antiretroviral therapy. All patients should have a baseline CD4 cell count at entry into care (AI); many authorities recommend two baseline measurements before decisions are made to initiate antiretroviral therapy because of wide variations in results (CIII). The test should be repeated yet a third time if discordant results are seen (AI). Recommendations for initiation of antiretroviral therapy based on CD4 cell count are found below in the "When to Treat: Indications for Antiretroviral Therapy" section.

Use of CD4+ T Cell Count for Monitoring Therapeutic Response

Adequate viral suppression for most patients on therapy is defined as an increase in $CD4^+$ cell count that averages 100 to 150 cells/mm^3 per year with an accelerated response in the first three months. This is largely because of redistribution. Subsequent increases with good virologic control show an average increase of approximately 100 cells/mm^3 per year for the subsequent few years until a threshold is reached.

Frequency of CD4+ T Cell Count Monitoring

In general, $CD4^+$ count should be determined every three to six months to (1) determine when to start antiretroviral in patients who do not meet the criteria for initiation; (2) assess immunologic response to antiretroviral therapy; and (3) assess the need for initiating chemoprophylaxis for opportunistic infections.

Viral Load

Plasma HIV RNA (viral load) may be a consideration in the decision to initiate therapy. In addition, viral load is critical for evaluating response to therapy (AI). Three HIV viral load assays have been approved by the U.S. Food and Drug Administration (FDA) for clinical use:

- HIV-1 reverse transcriptase polymerase chain reaction assay (Amplicor HIV-1 Monitor Test, version 1.5, Roche Diagnostic)

- Nucleic acid amplification test for HIV RNA (NucliSens HIV-1 QT, bioMerieux); and
- Signal amplification nucleic acid probe assay (VERSANT HIV-1RNA 3.0 assay, Bayer)

One key goal of therapy is a viral load below the limits of detection (at <50 copies/mL for the Amplicor assay, <75 copies/mL for the VERSANT assay, and <80 copies/mL for the NucliSens assay). This goal should be achieved by 16 to 24 weeks (AI). Recommendations for the frequency of viral load monitoring are summarized below and in Table 2 of the original guideline document.

At Initiation or Change in Therapy

Plasma viral load should be measured immediately before treatment and at 2 to 8 weeks after treatment initiation or treatment changes because of suboptimal viral suppression. In the latter measure, there should be a decrease of at least a 1.0 $\log_{10}$ copies/mL (BI).

In Patients With Viral Suppression Where Changes are Motivated by Drug Toxicity or Regimen Simplification

Some experts also recommend repeating viral load measurement within 2 to 8 weeks after changing therapy. The purpose of viral load monitoring at this point is to confirm potency of the new regimen (BII).

In Patients on a Stable Antiretroviral Regimen

The viral load testing should be repeated every 3 to 4 months thereafter or if clinically indicated (BII). (See Table 2 in the original guideline document.)

Monitoring Patients with Suboptimal Response

In addition to viral load monitoring, a number of additional factors should be assessed, such as non-adherence, altered pharmacology, or drug interactions. Resistance testing may be helpful in identifying the presence of resistance mutations that may necessitate a change in therapy (AII).

Utilization of Drug Resistance Testing in Clinical Practice

Panel's Recommendations

- HIV drug resistance testing is recommended for persons with acute HIV infection if the decision is made to initiate therapy at this time (BIII). If therapy is deferred, resistance testing at this time should still be considered (CIII).
- Drug resistance testing is also recommended for persons with chronic HIV infection prior to initiation of therapy (BIII). Earlier testing may be considered (CIII).
- A genotypic assay is generally preferred for antiretroviral-naïve persons (BIII).

- HIV drug resistance testing should be performed to assist in selecting active drugs when changing antiretroviral regimens in cases of virologic failure (BII).
- Drug resistance testing should also be considered when managing suboptimal viral load reduction (BIII).
- Drug resistance testing in the setting of virologic failure should be performed while the patient is taking his/her antiretroviral drugs, or immediately (i.e., within 4 weeks) after discontinuing therapy (BII).
- Drug resistance testing is not advised for persons with viral load <1,000 copies/mL, because amplification of the virus is unreliable (DIII).

Use of Resistance Assays in Pregnant Patients

In pregnant women, the purpose of antiretroviral therapy is to reduce plasma HIV RNA to less than the limit of detection, for the benefit of both mother and child. Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy and for those entering pregnancy with detectable HIV RNA levels while on therapy. Optimal prevention of perinatal transmission may require initiation of antiretroviral therapy before results of resistance testing are available.

Treatment Goals

Once the decision is made to initiate therapy, the primary goals of antiretroviral therapy are to:

- Reduce HIV-related morbidity and mortality
- Improve quality of life
- Restore and preserve immunologic functions
- Maximally and durably suppress viral load

Strategies to Achieve Treatment Goals

Achieving treatment goals requires a balance of sometimes competing considerations, outlined below. Providers and patients must work together to define priorities and determine treatment goals and options. See the original guideline document for more information on these topics.

- Selection of Combination Regimen
- Preservation of Future Treatment Options
- Pretreatment Drug Resistance Testing
- Drug Sequencing
- Improving Adherence

When to Treat: Indications for Antiretroviral Therapy

Panel's Recommendations (see Table 5 in the original guideline document)

- Antiretroviral therapy is recommended for all patients with history of an acquired immunodeficiency syndrome (AIDS)-defining illness or severe symptoms of HIV infection regardless of $CD4^+$ T cell count (AI).

- Antiretroviral therapy is also recommended for asymptomatic patients with <200 $CD4^+$ T cells/mm^3 (AI).
- Asymptomatic patients with $CD4^+$ T cell counts of 201 to 350 cells/mm^3 should be offered treatment (BII).
- For asymptomatic patients with $CD4^+$ T cell of >350 cells/mm^3 and plasma HIV RNA >100,000 copies/mL most experienced clinicians defer therapy but some clinicians may consider initiating treatment (CII).
- Therapy should be deferred for patients with $CD4^+$ T cell counts of >350 cells/mm^3 and plasma HIV RNA <100,000 copies/mL (DII).

The decision to begin therapy for the asymptomatic patient is complex and must be made in the setting of careful patient counseling and education.

Benefits and Risks of Treatment

Refer to the "Potential Benefits" and "Potential Harms" fields in this summary or see the original guideline document.

What to Start With: Initial Combination Regimens for the Antiretroviral-Naïve Patient

Summary of Recommended Regimens

To date, most clinical experience with combination therapy in treatment-naïve individuals is based on two different types of combination regimens, namely: non-nucleoside reverse transcriptase inhibitor (NNRTI)-based (1 NNRTI + 2 nucleoside reverse transcriptase inhibitors [NRTI]) and protease inhibitors (PI)-based (1 to 2 PI + 2 NRTI) regimens. Recommendations are, accordingly, organized by these categories.

A list of Panel-recommended components for initial therapy in treatment naïve patients can be found in Table 6a of the original guideline document. Column A lists the preferred and alternative NNRTI and PI components, and Column B lists the preferred and alterative dual-NRTI components. To construct a complete three- or four-drug antiretroviral regimen, one component should be selected from Column A and one from Column B. Table 6b in the original guideline document lists other antiretroviral components that are inferior to preferred or alternative components but may be used as initial therapy under special circumstances. A list of agents or components not recommended for initial treatment can be found in Table 7 in the original guideline document. Some agents or components not generally recommended for use because of lack of potency or potential serious safety concerns are listed in Table 8 in the original guideline document.

Potential advantages and disadvantages for each regimen recommended for initial therapy for treatment of naïve patients are listed in Table 9 of the original guideline document to guide prescribers in choosing the regimen best suited for an individual patient.

Factors to Consider When Selecting an Initial Regimen

The Panel affirms that regimen selection should be individualized, taking into consideration a number of factors including:

- Co-morbidity or conditions such as tuberculosis, liver disease, psychiatric disease, cardiovascular disease, chemical dependency, or pregnancy
- Adherence potential
- Dosing convenience regarding pill burden, dosing frequency, and food and fluid considerations
- Potential adverse drug effects
- Potential drug interactions with other medications
- Pregnancy potential
- Results of genotypic drug resistance testing
- Gender and pretreatment $CD4^+$ T cell count if considering nevirapine

Insufficient Data for Recommendations

Current data are insufficient to recommend a number of other combinations that are under investigation, such as NRTI-sparing regimens (e.g., NNRTI + PI or ritonavir-boosted PI monotherapy), quadruple-class regimens (e.g., NRTI + NNRTI + PI + entry inhibitor [EI] combinations): regimens containing EI as part of initial therapy; quadruple-NRTI regimens; regimens containing five or more active agents; and other novel strategies in treatment-naïve patients.

Not Recommended Strategies

Triple-class (e.g., NRTI + NNRTI + PI) regimens and a triple NRTI + NNRTI regimen showed no benefit over standard regimens.

NNRTI-Based Regimens (1 NNRTI + 2 NRTIs)

Panel's Recommendations

- Preferred NNRTI:
  - Efavirenz (except during first trimester of pregnancy or in women with high pregnancy potential*) (AII)
- Alternative NNRTI:
  - Nevirapine may be used as an alternative in adult females with $CD4^+$ T cell counts $\leq$250 cells/mm^3 and adult males with $CD4^+$ T cell counts $\leq$400 cells/mm^3 (BII).

*Women with high pregnancy potential are those who are trying to conceive or who are not using effective and consistent contraception.

PI-Based Regimens (1 or 2 PIs + 2 NRTIs)

Panel's Recommendations

Preferred PIs:

- Atazanavir + ritonavir* (AIII)
- Fosamprenavir + ritonavir* twice-daily (AII)

- Lopinavir/ritonavir (co-formulated) twice-daily (AII)

Alternative PIs:

- Atazanavir** (BII)
- Fosamprenavir (BII)
- Fosamprenavir + ritonavir* once-daily (BII)
- Lopinavir/ritonavir + (co-formulated) once-daily (BII)

Other Possible Options:

- Nelfinavir (CII)
- Saquinavir + ritonavir* (CII)

* Ritonavir at daily doses of 100 to 400 mg used as a pharmacokinetic-booster.

** Ritonavir 100 mg per day is recommended when tenofovir is used with atazanavir.

Dual-Nucleoside Options as Part of Initial Combination Therapy

Panel's Recommendations

Preferred Dual-NRTI:

- Tenofovir/emtricitabine* (co-formulated) (AII)
- Zidovudine/lamivudine* (co-formulated) (AII)

Alternative Dual-NRTI:

- Abacavir/lamivudine* (co-formulated) (BII)
- Didanosine + (lamivudine or emtricitabine) (BII)

Other Possible Option:

- Stavudine + lamivudine* (CII)

*Emtricitabine may be used in place of lamivudine or vice versa.

What Not to Use: (See Table 8 in the original guideline document)

Some antiretroviral regimens or components are not generally recommended because of suboptimal antiviral potency, unacceptable toxicity, or pharmacological concerns. These are summarized below.

Antiretroviral Regimens Not Recommended

Monotherapy (EII)

Single NRTI therapy does not demonstrate potent and sustained antiviral activity and should not be used.

Single-drug treatment regimens with a ritonavir-boosted PI, either lopinavir or atazanavir, are under investigation but cannot be recommended outside of a clinical trial at this time.

The rare, though controversial, exception is the use of zidovudine monotherapy to prevent perinatal HIV-1 transmission in a woman who does not meet clinical, immunologic, or virologic criteria for initiation of therapy and who has an HIV RNA <1,000 copies/mL (DIII). Most clinicians, however, prefer to use a combination regimen in the pregnant woman for the management of both the mother's HIV infection and in the prevention of perinatal transmission.

Dual Nucleoside Regimens (EII)

These regimens are not recommended because they have not demonstrated potent and sustained antiviral activity as compared with three-drug combination regimens.

Triple-NRTI Regimens (EII)

Except for abacavir/lamivudine/zidovudine (CII) and possibly zidovudine/lamivudine + tenofovir (DII), triple-NRTI regimens should NOT be used routinely because of suboptimal virologic activity or lack of data.

NRTI-Sparing Regimens (DII)

Because of pharmacokinetic interactions, drug toxicities, and drug resistance issues, these regimens (e.g., efavirenz together with indinavir or lopinavir/ritonavir) are not recommended routinely.

Antiretroviral Components Not Recommended (in alphabetical order) (See the original guideline document for more information on these components.)

- Amprenavir Oral Solution in Pregnant Women; Children <4 Years of Age; Patients with Renal or Hepatic Failure; and Patients Treated with Metronidazole or Disulfiram (EII)
- Amprenavir Oral Solution + Fosamprenavir (EIII)
- Amprenavir Oral Solution + Ritonavir Oral Solution (EIII)
- Atazanavir + Indinavir (EIII)
- Didanosine + Stavudine (EII)
- Efavirenz in First Trimester of Pregnancy and Women with Significant Childbearing Potential (EIII)
- Emtricitabine + Lamivudine (EIII)
- Nevirapine Initiated in Treatment-naïve Women with $CD4^+$ T Cell Counts >250 cells/mm^3 or in Treatment-naive Men with $CD4^+$ T Cell Counts >400 cells/mm^3 (DI)
- Saquinavir as a Single PI (i.e., unboosted) (EII)
- Stavudine + Zidovudine (EII)

<u>Limitations to Treatment Safety and Efficacy</u>

A number of factors may influence the safety and efficacy of antiretroviral therapy in individual patients. Examples include, but are not limited to: nonadherence to therapy, adverse drug reactions, drug-drug interactions, and development of drug resistance. Each is discussed in the original guideline document. Drug resistance, which has become a major reason for treatment failure, is discussed in greater detail in the section, "Management of the Treatment-Experienced Patient," below.

Management of the Treatment-Experienced Patient

Panel's Recommendations

- Virologic failure on treatment can be defined as a confirmed HIV RNA level >400 copies/mL after 24 weeks, >50 copies/mL after 48 weeks, or a repeated HIV RNA level >400 copies/mL after prior suppression of viremia to <400 copies/mL.
- Evaluation of antiretroviral treatment failure should include assessing the severity of HIV disease of the patient; the antiretroviral treatment history, including the duration, drugs used, antiretroviral potency, adherence history, and drug intolerance/toxicity; and the results of prior drug resistance testing.
- Drug resistance testing should be obtained while the patient is taking the failing antiretroviral regimen (or within 4 weeks of treatment discontinuation).
- In managing virologic failure, the provider should make a distinction between limited, intermediate, and extensive prior treatment exposure and resistance.
- The goal of treatment for patients with prior drug exposure and drug resistance is to re-establish maximal virologic suppression.
- For some patients with extensive prior drug exposure and drug resistance where viral suppression is difficult or impossible to achieve with currently available drugs, the goal of treatment is preservation of immune function and prevention of clinical progression.
- Assessing and managing a patient with extensive prior antiretroviral experience and drug resistance who is experiencing treatment failure is complex and expert advice is critical.

Definitions and Causes of Antiretroviral Treatment Failure

Antiretroviral treatment failure can be defined as a suboptimal response to therapy. Treatment failure is often associated with virologic failure, immunologic failure, and/or clinical progression (see below).

Many factors increase the likelihood of treatment failure, including:

- Baseline patient factors such as: earlier calendar year of starting therapy, higher pretreatment or baseline HIV RNA level (depending on the specific regimen used), lower pretreatment or nadir CD4 cell count, prior AIDS diagnosis, co-morbidities (e.g., depression, active substance use), presence of drug-resistant virus, prior treatment failure with development of drug resistance or cross resistance
- Incomplete medication adherence and missed clinic appointments
- Drug side effects and toxicity
- Suboptimal pharmacokinetics (variable absorption, metabolism, and/or penetration into reservoirs, food/fasting requirements, adverse drug-drug interactions with concomitant medications)

- Suboptimal potency of the antiretroviral regimen; and/or
- Other, unknown reasons

Virologic Failure can be defined as incomplete or lack of HIV RNA response to antiretroviral therapy:

- Incomplete virologic response: This can be defined as repeated HIV RNA >400 copies/mL after 24 weeks or >50 copies/mL by 48 weeks in a treatment-naïve patient initiating therapy. Baseline HIV RNA may impact the time course of response and some patients will take longer than others to suppress HIV RNA levels. The timing, pattern, and/or slope of HIV RNA decrease may predict ultimate virologic response. For example, most patients with an adequate virologic response at 24 weeks had at least a 1 $\log_{10}$ copies/mL HIV RNA decrease at 1 to 4 weeks after starting therapy.
- Virologic rebound: After virologic suppression, repeated detection of HIV RNA.

Immunologic Failure can be defined as failure to increase the CD4 cell count by 25 to 50 cells/mm^3 above the baseline count over the first year of therapy, or a decrease to below the baseline CD4 cell count on therapy. Mean increases in CD4 cell counts in treatment-naïve patients with initial antiretroviral regimens are approximately 150 cells/mm^3 over the first year. A lower baseline CD4 cell count may be associated with less of a response to therapy. For reasons not fully understood, some patients may have initial CD4 cell increases, but then minimal subsequent increases.

Clinical Progression can be defined as the occurrence or recurrence of HIV-related events (after at least 3 months on an antiretroviral regimen), excluding immune reconstitution syndromes. In one study, clinical progression (a new AIDS event or death) occurred in 7% of treated patients with virologic suppression, 9% of treated patients with virologic rebound, and 20% of treated patients who never achieved virologic suppression over 2.5 years.

Relationship Across Virologic Failure, Immunologic Failure, and Clinical Progression

Some patients demonstrate discordant responses in virologic, immunologic, and clinical parameters. In addition, virologic failure, immunologic failure, and clinical progression have distinct time courses and may occur independently or simultaneously. In general, virologic failure occurs first, followed by immunologic failure, and finally by clinical progression. These events may be separated by months to years.

Although heterogeneous, patients who experience treatment failure may be divided into those with

- Limited prior treatment and drug resistance who have adequate treatment options
- An intermediate amount of prior treatment and drug resistance with some available treatment options; and
- Extensive prior treatment and drug resistance who have some or no adequate treatment options

The assessment, goals of therapy, and approach to managing treatment failure differ for each of these three groups.

Assessment of Antiretroviral Treatment Failure and Changing Therapy

In general, the cause of treatment failure should be explored by reviewing the medical history and performing a physical examination to assess for signs of clinical progression. Important elements of the medical history include change in HIV RNA and CD4 cell count over time; occurrence of HIV-related clinical events; antiretroviral treatment history and results of prior resistance testing (if any); medication-taking behavior, including adherence to recommended drug doses, dosing frequency, and food/fasting requirements; tolerance of the medications; concomitant medications (with consideration for adverse drug-drug interactions); and comorbidities (including substance use). In many cases the cause(s) of treatment failure will be readily apparent. In some cases, no obvious cause may be identified.

For more information about the approach to treatment failure, see Table 23 in the original guideline document and "Novel strategies to consider for treatment-experienced patients with few available active treatment options" and "Treatment options following virologic failure on antiretroviral therapy regimens," below.

Initial Assessment of Treatment Failure

In conducting the assessment of treatment failure, it is important to distinguish among the reasons for treatment failure because the approaches to subsequent treatment will differ. The following assessments should be initially undertaken:

- Adherence. Assess the patient's adherence to the regimen. For incomplete adherence, identify and address the underlying cause(s) for non-adherence (e.g., access to medications, depression, active substance use), and simplify the regimen if possible (e.g., decrease pill count or dosing frequency) (AIII). (See "Adherence" in the original guideline document).
- Medication Intolerance. Assess the patient's side effects. Address and review the likely duration of side effects (e.g., the limited duration of gastrointestinal symptoms with some regimens). Management strategies for intolerance may include:
    - Use symptomatic treatment (e.g. antiemetics, antidiarrheals).
    - Change one drug to another within the same drug class, if needed (e.g., change to tenofovir for zidovudine-related gastrointestinal symptoms or anemia; change to nevirapine for efavirenz-related central nervous system symptoms) (AII).
    - Change drug classes (e.g., from a PI to an NNRTI or vice versa) if necessary (AII).
- Pharmacokinetic Issues. Review food/fasting requirements for each medication. Review recent history of gastrointestinal symptoms (such as vomiting or diarrhea) to assess the likelihood of short-term malabsorption. Review concomitant medications and dietary supplements for possible adverse drug-drug interactions and make appropriate substitutions for antiretroviral agents and/or concomitant medications, if possible (AIII). (See also "Therapeutic Drug Monitoring" in the original guideline document.)

- Suspected Drug Resistance. Obtain resistance testing while the patient is taking the failing regimen or within 4 weeks after regimen discontinuation (see "Utilization of Drug Resistance in Clinical Practice" in the original guideline document).

Subsequent Assessment of Treatment Failure

When adherence, tolerability, and pharmacokinetic causes of treatment failure have been considered and addressed, make an assessment for virologic failure, immunologic failure, and clinical progression.

1. Virologic Failure. There is no consensus on the optimal time to change therapy for virologic failure. The most aggressive approach would be to change for any repeated, detectable viremia (e.g., two consecutive HIV RNA >400 copies/mL after suppression to <400 copies/mL in a patient taking the regimen). Other approaches allow detectable viremia up to an arbitrary level (e.g., 1,000 to 5,000 copies/mL). However, ongoing viral replication in the presence of antiretroviral drugs promotes the selection of drug resistance mutations and may limit future treatment options. Isolated episodes of viremia ("blips", e.g., single levels of 50 to 1,000 copies/mL) may simply represent laboratory variation and usually are not associated with subsequent virologic failure, but rebound to higher viral loads or more frequent episodes of viremia increase the risk of failure.

   When assessing virologic failure, one should distinguish between limited, intermediate, and extensive drug resistance, taking into account prior treatment history and prior resistance test results. Drug resistance tends to be cumulative for a given individual and thus all prior treatment history and resistance test results should be taken into account. Table 23 in the original guideline document provides potential management strategies in different clinical scenarios.

   - Prior Treatment With No Resistance Identified. Consider the timing of the drug resistance test (e.g., was the patient off antiretroviral medications?) and/or non-adherence. Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., in 2 to 4 weeks) to determine if a resistant strain emerges (CIII). Consider intensifying with one drug (e.g., tenofovir) (BII) or pharmacokinetic enhancement (use of ritonavir boosting of a protease inhibitor) (BII).
   - Limited Prior Treatment and Drug Resistance. The goal in this situation is to re-suppress HIV RNA levels maximally and prevent further selection of resistance mutations. With virologic failure, consider changing the treatment regimen sooner, rather than later, to minimize continued selection of resistance mutations. Change at least 2 drugs in the regimen to active agents (BII). A single drug substitution (made on the basis of resistance testing) can be considered, but is unproven in this setting (CIII).
   - Intermediate Prior Treatment and Drug Resistance. The goal in this situation usually is to re-suppress HIV RNA levels maximally and prevent further selection of resistance mutations. Change at least 2 drugs in the regimen to active agents (BII).

- Extensive Prior Treatment and Drug Resistance (see Table 23 in the original guideline document and "Novel strategies to consider for treatment-experienced patients with few available active treatment options" and "Treatment options following virologic failure on antiretroviral therapy regimens," below). The goal is to re-suppress the HIV RNA levels maximally; however, viral suppression may be difficult to achieve in some patients. In this case, the goal is to preserve immunologic function and prevent clinical progression (even with ongoing viremia). Even partial virologic suppression of HIV RNA >0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefits; however, this must be balanced with the ongoing risk of accumulating additional resistance mutations. It is reasonable to observe a patient on the same regimen, rather than changing the regimen (depending on the stage of HIV disease), if there are few or no treatment options (BII). There is evidence from cohort studies that continuing therapy, even in the presence of viremia and the absence of CD4 cell increases, decreases the risk of disease progression. Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained <10,000 to 20,000 copies/mL. In a patient with a lower CD4 cell count (e.g., <100 cells/mm^3), a change in therapy may be critical to prevent further immunologic decline and clinical progression and is therefore indicated (BIII). A patient with a higher CD4 cell count may not be at significant risk for clinical progression, so a change in therapy is optional (CIII). Discontinuing or briefly interrupting therapy (even with ongoing viremia) may lead to a rapid increase in HIV RNA, a decrease in CD4 cell count, and increases the risk for clinical progression and therefore is not recommended (DIII).

2. Immunologic Failure. Immunologic failure may warrant a change in therapy in the setting of suppressed viremia. Assessment should include an evaluation for other possible causes of immunosuppression (e.g., HIV-2, HTLV-1, HTLV-2 drug toxicity). The combination of didanosine and tenofovir has been associated with CD4 cell declines or blunted CD4 cell responses. In the setting of immunologic failure, it would be reasonable to change one of these drugs (BIII). Although some clinicians have explored the use of intensification with additional antiretroviral drugs or immune-based therapies (e.g., interleukin-2) to improve immunologic responses, such therapies remain unproven and generally should not be offered in the setting of immunologic failure (DII).
3. Clinical Progression. Consider the possibility of immune reconstitution syndromes that typically occur within the first 3 months after starting effective antiretroviral therapy and that may respond to anti-inflammatory treatment(s) rather than changing antiretroviral therapy. Clinical progression may not warrant a change in therapy in the setting of suppressed viremia (BIII).

Changing an Antiretroviral Therapy Regimen for Virologic Failure

Panel's Recommendations

- For the patient with virologic failure, perform resistance testing while the patient still is taking the drug regimen or within 4 weeks after regimen discontinuation (AII).

- Use the treatment history and past and current resistance test results to identify active agents (preferably at least two fully active agents) to design a new regimen (AII). A fully active agent is one likely to demonstrate antiretroviral activity on the basis of both the treatment history and susceptibility on drug-resistance testing.
- If at least two fully active agents cannot be identified, consider pharmacokinetic enhancement of protease inhibitors (with the exception of nelfinavir) with ritonavir (BII) and/or re-using other prior antiretroviral agents to provide partial antiretroviral activity (CIII).
- Adding a drug with activity against drug-resistant virus (e.g., a potent ritonavir-boosted PI) and a drug with a new mechanism of action (e.g., HIV entry inhibitor) to an optimized background antiretroviral regimen can provide significant antiretroviral activity (BII).
- In general, one active drug should not be added to a failing regimen because drug resistance is likely to develop quickly (DII). However, in patients with advanced HIV disease (e.g., CD4 <100) and higher risk of clinical progression, adding one active agent (with an optimized background regimen) may provide clinical benefits and should be considered (CIII).

General Approach (see Table 23 in the original guideline document and "Novel strategies to consider for treatment-experienced patients with few available active treatment options" and "Treatment options following virologic failure on antiretroviral therapy regimens," below).

Ideally, one should design a regimen with two or more fully active drugs (on the basis of resistance testing or new mechanistic class) (BII). Some antiretroviral drugs (e.g., NRTIs) may contribute partial antiretroviral activity to an antiretroviral regimen. Note that using "new" drugs that the patient has not yet taken may not be sufficient because of cross-resistance within drug classes that reduces drug activity. As such, drug potency is more important than the number of drugs prescribed.

Early studies of treatment-experienced patients identified factors associated with better virologic responses to subsequent regimens. They include lower HIV RNA at the time of therapy change, using a new (i.e., not yet taken) class of drugs (e.g., NNRTI, HIV entry inhibitors), and using ritonavir-boosted PIs in PI-experienced patients.

See the original guideline document for information on sequencing and cross resistance, and new agents.

Current Approach

In general, using a single active antiretroviral drug in a new regimen is not recommended because of the risk of rapidly developing resistance to that drug. However, in patients with advanced HIV disease with a high likelihood of clinical progression (e.g., a CD4 cell count less than 100/mm^3), adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits. Weighing the risks (e.g., selection of drug resistance) and benefits (e.g., antiretroviral activity) of using a single active drug

in the heavily treatment-experienced patient is complicated, and consultation with an expert is advised.

Note from the National Guideline Clearinghouse (NGC): The following section is from Table 24 of the original guideline document.

Novel Strategies to Consider for Treatment-Experienced Patients with Few Available Active Treatment Options

- Pharmacokinetic enhancement with ritonavir may increase drug concentrations of most PIs (except nelfinavir) and may overcome some degree of drug resistance (CII).
- Therapeutic Drug Monitoring may be considered (see "Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents," below).
- Re-treating with prior medications may be useful, particularly if they were discontinued previously for toxicities that can now be better addressed (BII). Reusing prior medications (even with documented drug resistance) may provide some degree of partial antiretroviral activity. Continued drug therapy and maintenance of drug-resistant virus may compromise viral fitness, but it is not known if this has clinical applicability.
- The use of empiric multi-drug regimens (including up to 3 PIs and/or 2 NNRTIs) has been advocated by some, but may be limited ultimately by complexity, poor tolerability, and unfavorable drug-drug interactions (CII).
- New antiretroviral drugs (drugs in existing classes with activity against resistant viral strains, or new drug classes with novel mechanisms of action) including those available on expanded access (see Table 30 in the original guideline document) or through clinical trials may be used. For example, the PIs darunavir and tipranavir (in combination with low-dose ritonavir) were approved for use in treatment-experienced patients as part of a combination antiretroviral regimen based on providing superior antiretroviral activity to an investigator-selected comparator PI. The first approved HIV-1 entry inhibitor, enfuvirtide (T-20) was approved for use in the treatment-experienced patient with ongoing viremia on the basis of antiretroviral activity in this population. Optimally, a new active agent should be used with one or more other active agents in the regimen (e.g., a ritonavir-boosted PI and enfuvirtide) (BII).

Novel strategy not recommended at this time:

Structured treatment interruptions in the setting of virologic failure have been investigated prospectively, but most trials have shown limited or no virologic benefit. The risks of this approach (CD4 cell decline, HIV-related clinical events including death, acute retroviral syndrome) appear to outweigh any possible benefit (decreased HIV RNA levels on the next treatment regimen). Given the seriousness of the risks and the unproven benefits, this strategy cannot be recommended (DII).

Note from the National Guideline Clearinghouse (NGC): The following section is from Table 25 of the original guideline document.

Treatment Options Following Virologic Failure on Antiretroviral Therapy Regimens

First Virologic Failure:

Regimen Class	Initial Regimen	Recommended Change*
NNRTI	2 NRTIs + NNRTI	• 2 NRTIs (based on resistance testing) + PI (with or without low-dose ritonavir (AII)
PI	2 NRTIs + PI (with or without low-dose ritonavir)	• 2 NRTIs (based on resistance testing) + NNRTI (AII) • 2 NRTIs (based on resistance testing) + alternative PI (with low-dose ritonavir; based on resistance testing) (AII) • NRTI(s) (based on resistance testing) + NNRTI + alternative PI (with low-dose ritonavir; based on resistance testing) (AII)
Triple-NRTI	3 nucleosides	• 2 NRTIs (based on resistance testing) + NNRTI or PI (with or without low-dose ritonavir) (AIII) • NNRTI + PI (with or without low-dose ritonavir) (CIII) • NRTI(s) (based on resistance testing) + NNRTI + PI (with or without low-dose ritonavir) (CII)

Three-Class (NRTI, NNRTI, PI) Virologic Failure: >1 NRTIs (based on resistance testing) + a newer PI (with low-dose ritonavir; based on resistance testing) +/- enfuvirtide

(Note: NNRTIs generally should not be used following the development of NNRTI-resistance because of the risk for selection of additional NNRTI-associated mutations.)

* Antiretroviral therapy regimens should be selected on the basis of treatment history and drug-resistance testing to optimize antiretroviral potency in the second regimen. This is particularly important in selecting NRTIS for an NNRTI-based regimen where drug resistance may occur rapidly to the NNRTI if the NRTIs are not sufficiently potent.

Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents

Therapeutic drug monitoring (TDM) is a strategy applied to certain antiarrhythmics, anticonvulsants, and antibiotics to utilize drug concentrations to design regimens that are safe and will achieve a desired therapeutic outcome. Refer to the original guideline document for a detailed discussion of this topic including:

- TDM with PIs and NNRTIs
- TDM with NRTIs
- Scenarios for the use of TDM
- Use of TDM to Monitor Drug Concentrations
- Limitations to Using TDM in Patient Management

- TDM in Different Patient Populations (e.g., patients with wild-type virus, treatment-experienced patients)

A final caveat to the use of measured drug concentration in patient management is a general one: drug concentration information cannot be used alone; it must be integrated with other clinical and patient information. In addition, as knowledge of associations between antiretroviral concentrations and virologic response continues to accumulate, clinicians employing a TDM strategy for patient management should consult the most current literature.

Discontinuation or Interruption of Antiretroviral Therapy

Short-term Therapy Interruptions

- When all regimen components have similar half-lives and do not require food for proper absorption -- all drugs should be stopped simultaneously or may be given with a sip of water, if allowed. All discontinued regimen components should be restarted simultaneously.
- When all regimen components have similar half-lives and require food for adequate absorption, and the patient is required to take nothing by mouth for a sustained period of time -- temporary discontinuation of all drug components is indicated. The regimen should be restarted as soon as the patient can resume oral intake.
- When the antiretroviral regimen contains drugs with differing half-lives -- stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life (typically an NNRTI). Options in this circumstance are discussed below. (See "Discontinuation of efavirenz or nevirapine" in the original guideline document.)
- When a patient experiences a severe or life-threatening toxicity -- all components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

Interruption of Therapy after Pregnancy

HIV-infected pregnant women who otherwise do not meet current $CD4^+$ cell count criteria for starting treatment may initiate antiretroviral therapy primarily for the purpose of preventing mother-to-child HIV transmission. These women may desire to stop therapy after delivery. Discontinuation recommendations are in the current guidelines for pregnant women. (See "HIV-Infected Women of Reproductive Age and Pregnant Women" below.)

Planned Long-term Therapy Interruptions

- In patients who initiated therapy during acute HIV infection and achieved virologic suppression -- the optimal duration of treatment and the consequences of treatment discontinuation are not known at this time. (See "Acute HIV Infection" section below.)
- In patients who have had exposure to multiple antiretroviral agents, have experienced antiretroviral treatment failure, and have few treatment options available because of extensive resistance mutations -- interruption is generally not recommended unless it is done in a clinical trial setting. Several clinical trials, yielding conflicting results, have

been conducted to better understand the role of treatment interruption in these patients. The Panel notes that partial virologic suppression from combination therapy has been associated with clinical benefit; therefore, interruption of therapy should be avoided.

- In patients on antiretroviral therapy who have maintained a $CD4^+$ cell count above the level currently recommended for treatment initiation and whose baseline $CD4^+$ was either above or below that recommended threshold -- interruption is also not recommended unless it is done in a clinical trial setting. (See the original guideline document for discussion of potential adverse outcomes seen in some treatment interruption trials.)

Physicians and patients considering treatment interruption for any reason should be aware of the potential clinical consequences observed during some clinical and observational studies of treatment interruption strategies. The outcomes of these studies are not uniform, and there are important differences in their designs, including the study populations, duration of therapy, and thresholds for the resumption of treatment.

If therapy has to be discontinued, patients should be counseled about the need for close clinical and laboratory monitoring. They should also be aware of the risks of viral rebound, acute retroviral syndrome, decline of CD4 cell count, HIV disease progression, development of minor HIV-associated manifestations such as oral thrush, development of drug resistance, and the need for chemoprophylaxis against opportunistic infections depending on the $CD4^+$ T cell count. A timeline for restarting therapy should be discussed. Each patient should be counseled about the need to follow safe behavior guidelines to reduce the risk of HIV transmission. Data from relevant controlled trials should be shared with the patient.

Prior to any intentional treatment interruption, a number of antiretroviral-specific issues should be taken into consideration. These include

- Discontinuation of efavirenz or nevirapine. The optimal interval between stopping efavirenz or nevirapine and other antiretroviral drugs is not known. The duration of detectable levels of these drugs after discontinuation ranges from less than one week to over three weeks. Simultaneously stopping all drugs in a regimen containing these agents may result in functional monotherapy with the NNRTIs, because their half-lives are longer than other agents. This may increase the risk of selection of NNRTI-resistant mutations. It is further complicated by evidence that certain host genetic polymorphisms may result in slower rates of clearance. Such polymorphism may be more common among specific ethnic groups, such as African Americans and Hispanics. Some experts recommend stopping the NNRTI but continuing the other antiretroviral drugs for a period of time. The optimal time sequence for staggered component discontinuation has not been determined. A study in South Africa demonstrated that giving four or seven days of zidovudine plus lamivudine after a single dose of nevirapine reduced the risk of postnatal nevirapine resistance from 60% to 10% - 12%. An alternative strategy used by some experts is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time; however, no specific efficacy data supporting this have been reported. The optimal duration needed to continue the PI-based regimen after stopping the NNRTI is not known. Given the

prolonged potential of detectable NNRTI concentrations for more than three weeks, some suggest that the PI-based regimen may need to be continued for up to four weeks. Further research to determine the best approach to discontinuing NNRTIs is needed.

- Discontinuation and reintroduction of nevirapine. Because nevirapine is an inducer of the drug-metabolizing hepatic enzymes, administration of full therapeutic doses of nevirapine without a two-week, low-dose escalation phase will result in excess plasma drug levels and potentially increase the risk for toxicity. Therefore, in a patient who has interrupted treatment with nevirapine for more than two weeks and is to be restarted later, nevirapine should be reintroduced with a dose escalation period of 200 milligram once daily for 14 days, then a 200 milligram twice-daily regimen (AII).
- Discontinuation of emtricitabine, lamivudine, or tenofovir in patients with hepatitis B co-infection. Patients with hepatitis B co-infection (hepatitis B surface antigen or HBeAg positive) and receiving one or a combination of these NRTIs may experience an exacerbation of hepatitis upon drug discontinuation. If any of the above agents is discontinued, the patients should be closely monitored for exacerbation of hepatitis or for hepatic flare (AII). Some experts suggest initiating adefovir or entecavir* for the treatment of HBV in these patients (CIII). (See "Hepatitis B and HIV co-infection" section below.)

* 2007 Addendum

Note from the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents: Previously, the guidelines recommended entecavir as an option for patients who required treatment for Hepatitis B virus (HBV) but not HIV infection. This recommendation was based on in vitro data showing no significant activity of entecavir against HIV-1. A recent case series of three patients who received entecavir without concomitant antiretroviral therapy reported a 1 $\log_{10}$ decline in HIV-RNA levels and emergence of M184V mutations in one patient who was studied in detail.

Based on these preliminary findings, the Panel recommends that:

For HBV/HIV co-infected patients, entecavir should not be used for the treatment of HBV infection without concomitant treatment for HIV.

Considerations for Antiretroviral Use in Special Patient Populations

Acute HIV Infection

Panel's Recommendations

- Whether treatment of acute HIV infection results in long-term virologic, immunologic, or clinical benefit is unknown; treatment should be considered optional at this time (CIII).
- Therapy should also be considered optional for patients in whom HIV seroconversion has occurred within the previous 6 months (CIII).
- If the clinician and patient elect to treat acute HIV infection with antiretroviral therapy, treatment should be implemented with the goal of suppressing plasma HIV RNA levels to below detectable levels (AIII).

- For patients with acute HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels and $CD4^+$ T cell count and toxicity monitoring should be performed as described for patients with established, chronic HIV infection (AII).
- If the decision is made to initiate therapy in a person with acute HIV infection, genotypic resistance testing at baseline will likely optimize virologic response; this strategy is therefore recommended (BIII). If therapy is deferred, genotypic resistance testing should still be considered, because the result may be useful in optimizing the virologic response when therapy is ultimately initiated (CIII).

Diagnosis of Acute HIV Infection

Health care providers should consider a diagnosis of acute HIV infection for patients who experience a compatible clinical syndrome (see Table 27 in the original guideline document) and who report recent high risk behavior. In these situations, tests for plasma HIV RNA and HIV antibody should be obtained (BII). Acute HIV infection is defined by detectable HIV RNA in plasma by using sensitive PCR or bDNA assays in the setting of a negative or indeterminate HIV antibody test. A low-positive HIV RNA level (<10,000 copies/mL) may represent a false-positive test, since values in acute infection are generally very high (>100,000 copies/mL).

Patients with HIV infection diagnosed by HIV RNA testing should have confirmatory serologic testing performed at a subsequent time point (AI).

Data from the United States and Europe demonstrate that transmitted virus may be resistant to at least one antiretroviral drug in up to 16% of patients. If the decision is made to initiate therapy in a person with acute HIV infection, resistance testing at baseline will likely optimize virologic response; this strategy is therefore recommended (BIII). (See "Utilization of Drug Resistance Testing in Clinical Practice" section above.)

See Potential Benefits and Harms sections in this summary for information on potential benefits and risks of treating acute HIV infection.

HIV-Infected Adolescents

Antiretroviral Therapy Considerations in Adolescents. Adult guidelines for antiretroviral therapy are usually appropriate for post pubertal adolescents because HIV-infected adolescents who were infected sexually or through injecting-drug use during adolescence follow a clinical course that is more similar to that of adults than to that of children.

Dosage for medications for HIV infection and opportunistic infections should be prescribed according to Tanner staging of puberty and not on the basis of age. Adolescents in early puberty (i.e., Tanner Stage I and II) should be administered doses using pediatric schedules, whereas those in late puberty (i.e., Tanner Stage V) should follow adult dosing schedules. Because puberty may be delayed in perinatally-HIV infected children, continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than usual adult doses. Since data are not available to predict optimal medication doses for

each antiretroviral medication for this group of children, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered in determining when to transition from pediatric to adult doses. Youth who are in their growth spurt (i.e., Tanner Stage III in females and Tanner Stage IV in males) using adult or pediatric dosing guidelines and those adolescents whose doses have been transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity.

Adherence Concerns in Adolescents. HIV-infected adolescents have specific adherence problems. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents, who are frequently inexperienced with health-care systems.

For a more detailed discussion on specific issues on therapy and adherence for HIV-infected adolescents see the National Guideline Clearinghouse (NGC) summary: Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection.

Special Considerations in Adolescent Females

Gynecological care is especially difficult to provide for the HIV infected female adolescent but is a critical part of their care. Because many adolescents with HIV infection are sexually active, contraception and prevention of HIV transmission should be discussed with the adolescent, including the interaction of specific antiretroviral drugs on birth control pills. The potential for pregnancy may also alter choices of antiretroviral therapy. As an example, efavirenz should be used with caution in females of child bearing age and should only be prescribed after intensive counseling and education about the potential effects on the fetus, the need for close monitoring including periodic pregnancy testing and a commitment on the part of the teen to use effective contraception. For a more detailed discussion, see "HIV-Infected Women of Reproductive Age and Pregnant Women," below.

Given the lifelong infection with HIV and the need for treatment through several stages of growth and development, HIV care programs and providers need to support this appropriate transition in care for HIV-infected infants through adolescents.

Injection Drug Users (IDUs)

See the original guideline document for information about the challenges of treating IDUs infected with HIV, the efficacy of HIV treatment in IDUs, and IDU/HIV drug toxicities and interactions.

Provision of successful antiretroviral therapy for injection drug users is possible. It is enhanced by supportive clinical care sites and provision of drug treatment, awareness of interactions with methadone and the increased risk of side effects and toxicities and the need for simple regimens to enhance medication adherence. These are important considerations in selection of regimens and providing appropriate patient monitoring in this population. Preference should be given to antiretroviral agents with lower risk for hepatic and neuropsychiatric side effects, simple dosing schedules, and lack of interaction with methadone.

HIV-Infected Women of Reproductive Age and Pregnant Women

Panel's Recommendations

- When initiating antiretroviral therapy for women of reproductive age, the indications for initiation of therapy and the goals of treatment are the same as for other adults and adolescents (AI).
- Efavirenz should be avoided for the woman who desires to become pregnant or who does not use effective and consistent contraception (AIII).
- For the woman who is pregnant, an additional goal of therapy is prevention of mother-to-child transmission (PMTCT), with a goal of viral suppression to <1,000 copies/mL to reduce the risk of transmission of HIV to the fetus and newborn (AI).
- Selection of an antiretroviral combination should take into account known safety, efficacy, and pharmacokinetic data of each agent during pregnancy (AIII).
- Clinicians should consult the most current Public Health Services guidelines when designing a regimen for a pregnant patient (AIII).

Women of Reproductive Age

In women of reproductive age, antiretroviral regimen selection should account for the possibility of planned or unplanned pregnancy. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans, and use of effective contraception should be discussed with the patient. As part of the evaluation for initiating therapy, women should be counseled about the potential teratogenic risk of efavirenz-containing regimens should pregnancy occur. These regimens should be avoided in women who are trying to conceive or are not using effective and consistent contraception. Various PIs and NNRTIs are known to interact with oral contraceptives, resulting in possible decreases in ethinyl estradiol or increases in estradiol or norethindrone levels (see Table 21 in the original guideline document). These changes may decrease the effectiveness of the oral contraceptives or potentially increase risk of estrogen- or progestin-related side effects. Providers should be aware of these drug interactions and an alternative or additional contraceptive method should be considered. Amprenavir (and probably fosamprenavir) not only increases blood levels of both estrogen and progestin components, but oral contraceptives decrease amprenavir levels as well; these drugs should not be co-administered. There is minimal information about drug interactions with use of newer hormonal contraceptive methods (e.g., patch, vaginal ring). Counseling should be provided on an ongoing basis. Women who express a desire to become pregnant should be referred for pre-conception counseling and care, including discussion of special considerations with antiretroviral therapy use during pregnancy.

Pregnant Women

Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to prevention of mother-to-child transmission (PMTCT) and to maternal and fetal safety, timing of initiation of treatment and selection of regimens may be different from non-pregnant adults or adolescents.

PMTCT

Antiretroviral therapy is recommended in all pregnant women, regardless of virologic, immunologic, or clinical parameters, for the purpose of PMTCT (AI).

The decision to use any antiretroviral drug during pregnancy should be made by the woman after discussion with her clinician regarding the benefits versus risks to her and her fetus. Long-term follow-up is recommended for all infants born to women who have received antiretroviral drugs during pregnancy regardless of the infants' HIV status.

Regimen Considerations

See Table 28 in the original guideline document for short- and long-term effects of the antiretroviral drugs on the fetus and newborn. Based on available data, recommendations related to drug choices have been developed by the U.S. Public Health Service Task Force and can be found in Table 29 of the original guideline document.

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to antiretroviral drugs (either administered alone or in combinations) to the Antiretroviral Pregnancy Registry (Telephone: 910-251-9087 or 1-800-258-4263). The registry collects observational, non-experimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing potential teratogenicity. For more information regarding selection and use of antiretroviral therapy during pregnancy, please refer to the NGC summary: Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States.

Lastly, the women should be counseled regarding the avoidance of breastfeeding. Continued clinical, immunologic, and virologic follow-up should be done as recommended for non-pregnant adults and adolescents.

Discontinuation of Antiretroviral Therapy Post-Partum

Pregnant women who are started on antiretroviral therapy during therapy for the sole purpose of PMTCT and who do not meet criteria for starting treatment for their own health may choose to stop antiretroviral therapy after delivery. However, if therapy includes nevirapine, stopping all regimen components simultaneously may result in functional monotherapy because of its long half-life and subsequent increased risk for resistance. Nevirapine resistance mutations have been identified postpartum in women taking nevirapine-containing combination regimens only for prevention of mother-to-child transmission. In one study nevirapine resistance was identified in 16% of women despite continuation of the nucleoside backbone for 5 days after stopping nevirapine. Further research is needed to assess appropriate strategies for stopping nevirapine-containing combination regimens after delivery in situations where ongoing maternal treatment is not indicated.

Antiretroviral Considerations in Patients with Co-Infections

Treatment Recommendations for HIV/HBV Co-infected Patients

- All patients with HBV should be advised to avoid alcohol; should receive hepatitis A vaccine, if found not to be immune at baseline (i.e., absence of hepatitis A antibody); should be advised on methods to prevent HBV transmission; and should be evaluated for the extent of HBV infection.
- Need to treat HIV and not HBV: The combination of tenofovir + emtricitabine or tenofovir + lamivudine can be used as the NRTI backbone of an antiretroviral regimen. Lamivudine, tenofovir, or emtricitabine should not be the only agents with anti-HBV activity in a regimen, to avoid development of HBV-resistant mutants.
- Need to treat HIV and HBV: The combination of tenofovir + lamivudine or tenofovir + emtricitabine should be considered as first-choice NRTI backbones. Additional options include entecavir* alone or in combination with one of the three nucleosides with activity against both viruses. The use of lamivudine, emtricitabine, or tenofovir as the only active anti-HBV agent should be avoided because of the risk of resistance.
- Treatment of HBV and not HIV: Pegylated interferon-alpha is an option that does not lead to development of drug-resistant HIV or HBV mutants. Entecavir* is a nucleoside analogue that is not active against HIV, so it is another option in this situation. Adefovir dipivoxil is active against HBV but not against HIV at the 10 milligram dose; however, a theoretical risk for development of HIV mutants exists, because it is related to tenofovir. The use of emtricitabine, lamivudine, or tenofovir without a full HAART regimen should be avoided because of the rapid development of drug-resistant HIV mutations.
- Need to discontinue lamivudine, tenofovir, or emtricitabine: Monitor clinical course with frequent liver function tests, and consider the use of adefovir dipivoxil or entecavir to prevent flares, especially in patients with marginal hepatic reserve.

* 2007 Addendum

Note from the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents: Previously, the guidelines recommended entecavir as an option for patients who required treatment for Hepatitis B virus (HBV) but not HIV infection. This recommendation was based on in vitro data showing no significant activity of entecavir against HIV-1. A recent case series of three patients who received entecavir without concomitant antiretroviral therapy reported a 1 $\log_{10}$ decline in HIV-RNA levels and emergence of M184V mutations in one patient who was studied in detail.

Based on these preliminary findings, the Panel recommends that:

For HBV/HIV co-infected patients, entecavir should not be used for the treatment of HBV infection without concomitant treatment for HIV.

Hepatitis C (HCV)/HIV Co-Infection

Assessment of HCV/HIV Co-Infection. Patients with HIV/HCV infection should be advised to avoid or limit alcohol consumption, use appropriate precautions to prevent transmission of both viruses to others, and should be given hepatitis A

and B vaccine if found to be susceptible. All patients with HCV, including those with HIV co-infection, should be evaluated for HCV therapy.

Standard indications for HCV therapy in the absence of HIV infection are detectable plasma HCV RNA and a liver biopsy showing bridging or portal fibrosis. ALT levels may be elevated in association with HCV infection. However, ALT levels do not accurately reflect the severity of HIV-associated liver disease. Liver biopsy is important for HCV therapeutic decision making but is indicated only if the patient is considered a treatment candidate based on multiple other variables including severity and stability of HIV disease, other comorbidities, probability of adherence, and if there are contraindications to interferon-alpha, one of the drugs available for treatment of HCV.

Clinical trials in patients with HCV/HIV co-infection using pegylated interferon plus ribavirin for 48 weeks show sustained virologic response (SVR) rates of 60 to 70% for HCV genotype 2/3 but only 15 to 28% for genotype 1. These data are based on experience almost exclusively in carefully selected patients with $CD4^+$ T cell counts over 200 cells/mm^3.

Treatment of HCV/HIV Co-Infection. Based on these observations, treatment of HCV is recommended according to standard guidelines with preference for those with higher CD4 cell counts (>200 cells/mm^3). For some patients with lower CD4 counts, it may be preferable to initiate antiretroviral therapy and delay HCV therapy. Concurrent treatment is feasible, but may be complicated by pill burden, drug toxicities, and drug interactions.

Scenarios for Treating HCV/HIV Co-Infection. Differences in HCV therapy management in the presence of HIV co-infection include:

- Ribavirin should not be given with didanosine due to the potential for drug-drug interactions leading to pancreatitis and lactic acidosis.
- Some NRTIs and all NNRTIs and PIs are potentially hepatotoxic so that monitoring of serum transaminase levels is particularly important.
- Zidovudine combined with ribavirin is associated with higher rates of anemia suggesting this combination be avoided when possible.
- Growth factors to manage interferon-associated neutropenia and ribavirin-associated anemia may be required.

Mycobacterium Tuberculosis (TB/HIV Co-Infection)

Panel's Recommendations

- The treatment of tuberculosis in patients with HIV infection should follow the same principles for persons without HIV infection (AI).
- Presence of active tuberculosis requires immediate initiation of treatment (AI).
- In antiretroviral-naïve patients, delay of antiretroviral therapy for 4-8 weeks after initiation of tuberculosis treatment permits a better definition of causes of adverse reactions and paradoxical reactions (BIII).
- Directly observed therapy is strongly recommended for HIV/TB co-infected patients (AII).

- Rifampin/rifabutin-based regimens should be given at least three times weekly in patients with $CD4^+$ T cell count <100 cells/mm^3 (AII).
- Once weekly rifapentine is not recommended in HIV-infected patients (EI).
- Despite drug interactions, rifamycin should be included in patients receiving anti-retroviral therapy, with dosage adjustment as necessary (AII).
- Paradoxical reaction should be treated with continuation of treatment for tuberculosis and HIV, along with use of non-steroidal anti-inflammatory agents (BIII).
- In severe cases of paradoxical reaction, some suggest use of high dose prednisone (CIII).

Treatment of Tuberculosis

Treatment of drug-susceptible tuberculosis should consist of the standard regimen outlined in treatment guidelines, which consist of isoniazid (INH), rifampin or rifabutin (RIF), pyrazinamide (PZA), and ethambutol (EMB) or streptomycin (SM) given two months followed by INH + RIF for 4 to 7 months (AI). Special attention should be given to the potential of drug-drug interactions with rifamycin as discussed below. In the case of single or multi-drug resistant tuberculosis, therapy should be prescribed based on susceptibility, preferably in consultation with tuberculosis experts.

Directly Observed Therapy (DOT). DOT is strongly recommended for patients with HIV/TB coinfection (AII). Once or twice-weekly dosing has been associated with increased rates of rifamycin resistance in patients with advanced HIV. Thus, once-weekly rifapentine is not recommended (EI) and rifampin/rifabutin-based TB regimens should be given at least three times weekly for those with a $CD4^+$ T cell count <100 cells/mm^3 (AII). In general, daily DOT is recommended for the first two months and then three times weekly DOT for the continuation phase (BII).

Anti-tuberculosis/Antiretroviral Drug Toxicities and Interactions. All antiretroviral drugs are associated with the potential for hepatotoxicity. INH, RIF, and PZA may also cause drug-induced hepatitis. These first line anti-tuberculous drugs should be used if at all possible even with coadministration of other hepatotoxic drug or baseline liver disease (AIII). Patients receiving these drugs should have frequent monitoring for clinical symptoms of hepatitis and laboratory monitoring for hepatotoxicity, including serum aminotransferases, bilirubin, and alkaline phosphatase.

Prevention Counseling for the HIV-Infected Patient

Prevention counseling is an essential component of management for HIV-infected persons. Each patient encounter provides an opportunity to reinforce HIV prevention messages. Therefore, each encounter should include assessment and documentation of:

- Patient's knowledge and understanding of HIV transmission
- Patient's HIV transmission behaviors since the last encounter with a member of the health-care team

This should be followed by a discussion of strategies to prevent transmission that might be useful to the patient. Each member of the health care team can routinely

provide this counseling. Partner notification is a key component of HIV detection and prevention and should be pursued with the patient by the provider or by referral services.

Definitions:

Strength of the Evidence

Categories reflecting the quality of evidence supporting the recommendations:

I. At least one randomized trial with clinical results
II. Clinical trials with laboratory results
III. Expert opinion

Strength of Recommendation

A. Strong
B. Moderate
C. Optional
D. Should usually not be offered
E. Should never be offered

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

Recommendations are based upon expert opinion and scientific evidence. When appropriate data are not available, inconclusive, or contradictory, the recommendation is based on "expert opinion."

2007 Addendum

The recommendation is based on evidence from a recent case series.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Overall Benefits

The primary goals of antiretroviral therapy are to reduce human immunodeficiency virus (HIV)-related morbidity and mortality, improve quality of

life, restore and preserve immunologic function, and maximally and durably suppress viral load.

Specific Benefits

Potential Benefits of Deferred Therapy

- Avoidance of treatment-related negative effects on quality of life and drug-related toxicities
- Preservation of treatment options
- Delay in the development of treatment resistance if there is incomplete viral suppression
- More time for the patient to have a greater understanding of treatment demands
- Decreased total time on medication with reduced chance of treatment fatigue
- More time for the development of more potent, less toxic, and better studied combinations of antiretrovirals

Potential Benefits of Treating Acute Infection

Preliminary data indicate that treatment of acute HIV infection with combination antiretroviral therapy has a beneficial effect on laboratory markers of disease progression. Theoretically, early intervention could decrease the severity of acute disease; alter the initial viral setpoint, which can affect disease-progression rates; reduce the rate of viral mutation as a result of suppression of viral replication; preserve immune function; and reduce the risk for viral transmission.

POTENTIAL HARMS

Overall Harms

The risks of therapy for human immunodeficiency virus (HIV) infection include adverse effects on quality of life resulting from drug toxicities and dosing constraints; the potential, if therapy fails to effectively suppress viral replication, for the development of drug resistance, which may limit future treatment; and the potential need for continuing therapy indefinitely.

Specific Harms

Potential Risks of Deferred Therapy

- The possibility that damage to the immune system, which might otherwise be salvaged by earlier therapy, is irreversible
- The increased possibility of progression to acquired immune deficiency syndrome (AIDS)
- The increased risk for HIV transmission to others during a longer untreated period

Potential Risks of Treating Acute HIV Infection.

The potential disadvantages of initiating therapy include exposure to antiretroviral therapy without a known clinical benefit, which could result in drug toxicities, development of antiretroviral drug resistance, the need for continuous therapy, and adverse effect on quality of life.

Refer to the original guideline document, including Tables 17 through 19, for important and more detailed information regarding the adverse effects associated with antiretroviral drugs, highly active antiretroviral therapy, and potential drug interactions.

CONTRAINDICATIONS

CONTRAINDICATIONS

See Tables 19 to 21 in the original guideline document for drug combinations that should be avoided.

Some antiretroviral regimens or components are not recommended for human immunodeficiency virus type 1 (HIV-1) infected patients due to suboptimal antiviral potency, unacceptable toxicity, or pharmacological concerns. See "What Not to Use" in the "Major Recommendations" field for detailed information.

- Saquinavir mesylate is contraindicated as a single protease inhibitor (PI) because of poor bioavailability that averages only 4%, even with a concurrent high-fat meal.
- Amprenavir oral solution is contraindicated in pregnant women, children <4 years of age, patients with renal or hepatic failure, and patients treated with metronidazole or disulfiram.
- Efavirenz is contraindicated in the first trimester of pregnancy and in women with significant childbearing potential.
- Tipranavir/ritonavir is contraindicated in patients with moderate to severe (Child-Pugh class B & C) hepatic insufficiency.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The Panel has carefully reviewed recent results from clinical trials in human immunodeficiency virus (HIV) therapy and considered how they inform appropriate care guidelines. The Panel appreciates that HIV care is highly complex and rapidly evolving. Guidelines are never fixed and must always be individualized. Where possible, the Panel has based recommendations on the best evidence from prospective trials with defined endpoints. When such evidence does not yet exist, the panel attempted to reflect reasonable options in its conclusions.
- HIV care requires, as always, partnerships and open communication. The provider can make recommendations most likely to lead to positive outcomes only if the patient's own point of view and social context is well known. Guidelines are only a starting point for medical decision-making. They can identify some of the boundaries of high care quality, but cannot substitute for sound judgment.

- These recommendations are not intended to supersede the judgment of clinicians who are knowledgeable in the care of human immunodeficiency virus (HIV)-infected individuals.
- Information included in these guidelines may not represent U.S. Food and Drug Administration (FDA) approval or approved labeling for the particular products or indications in question. Specifically, the terms "safe" and "effective" may not be synonymous with FDA-defined legal standards for product approval.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Foreign Language Translations
Patient Resources
Personal Digital Assistant (PDA) Downloads
Pocket Guide/Reference Cards
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

RELATED QUALITY TOOLS

- AIDSinfo's Antiretroviral Toxicity Tool for PDAs

- AIDSinfo's Drug Database for Palm PDAs

- A Pocket Guide to Adult HIV/AIDS Treatment: Companion to A Guide to Primary Care of People with HIV/AIDS August 2004 Edition

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Bethesda (MD): Department of Health and Human Services (DHHS); 2006 Oct 10. 116 p. [340 references]

Panel on Antiretroviral Guidelines for Adults and Adolescents. Supplement to the guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents - October 10, 2006. Bethesda (MD): Department of Health and Human Services (DHHS); 2007 Apr 30. 1 p. [2 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 Dec 1 (updated 2006 Oct 10)

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Centers for Disease Control and Prevention - Federal Government Agency [U.S.]

SOURCE(S) OF FUNDING

United States Government

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Panel on Clinical Practices for Treatment of HIV Infection

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GUIDELINE STATUS

This is the current release of the guideline. It was last updated on October 10, 2006; an addendum was released April 30, 2007.

These guidelines generally represent the state of knowledge regarding the use of antiretroviral agents. However, as the science rapidly evolves, the availability of new agents and new clinical data may rapidly change therapeutic options and preferences. The guidelines are therefore updated frequently by the Panel, which meets monthly by teleconferencing to make ongoing revisions as necessary. All revisions are summarized and highlighted on the AIDSinfo Web site. Proposed revisions are posted for a public comment period, generally for 2 weeks, after which comments are reviewed by the Panel prior to finalization. Comments can be sent to aidsinfowebmaster@aidsinfo.nih.gov.

Status information regarding this guideline is available from the AIDSinfo Web site, telephone (800) 448-0440, fax (301) 519-6616; TTY (888) 480-3739.

GUIDELINE AVAILABILITY

Electronic copies of the guideline and addendum: Available in Portable Document Format (PDF) from the AIDSinfo Web site.

The guideline is also available for Palm OS or Pocket PC download from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: www.cdcnpin.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Adherence to potent antiretroviral therapy. 2004 Oct 29. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the AIDSinfo Web site. Also available as a Personal Digital Assistant (PDA) download from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: www.cdcnpin.org. Requests for print copies can also be submitted via the AIDSinfo Web site.

The following is also available:

- Clinical management of the HIV-infected adult. A manual for midlevel clinicians. 1993 Sep (revised 2006). .399 p. Electronic copies: Available in Portable Document Format (PDF) from the AIDSinfo Web site.

Print copies: Available from Southeast AIDS Training and Education Center, Emory University School of Medicine, 735 Gatewood Road, NE, Atlanta, GA 30322. Telephone: (404) 727-2929; fax (404) 727-4562. E-mail: seatec@emory.edu. Web site: www.seatec.emory.edu.

The following Power Point slide sets based on the "Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents" are also available:

- Comprehensive guideline summary. Guidelines for the use of antiretroviral agents in adults and adolescents. AIDS Education and Training Center (AETC) National Resource Center. Oct 2006. 46 slides. Available from the AETC Web site.
- Initiation of therapy. Guidelines for the use of antiretroviral agents in adults and adolescents. AIDS Education and Training Center (AETC) National Resource Center. Oct 2006. 58 slides. Available from the AETC Web site.
- Changing therapy. Guidelines for the use of antiretroviral agents in adults and adolescents. AIDS Education and Training Center (AETC) National Resource Center. Oct 2006. 37 slides. Available from the AETC Web site.

- Special issues. Guidelines for the use of antiretroviral agents in adults and adolescents. AIDS Education and Training Center (AETC) National Resource Center. May 2006. 55 slides. Available from the AETC Web site.

The following is also available:

- Antiretroviral Pocket Reference Cards. Antiretroviral therapy in adults and adolescents. AIDS Educational and Training Center (AETC) Sep 2006. Available from the AETC Web site.
- A comprehensive Spanish-language Web site featuring information about HIV treatment and clinical trials is available at http://aidsinfo.nih.gov/infoSIDA/.

PATIENT RESOURCES

The following is available:

- HIV and its treatment: what you should know. Bethesda (MD): Department of Health and Human Services (DHHS); 2006 Aug. 15 p.

Electronic copies: Available in Portable Document Format (PDF) from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: http://www.cdcnpin.org.

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This summary was completed by ECRI on July 20, 1999. The original information was verified by the guideline developer on August 10, 1999. Updated guidelines were issued on January 28, 2000, February 5, 2001, April 23, 2001, August 17, 2001, February 4, 2002, July 14, 2003, November 10, 2003, November 17, 2003, and March 29, 2004. This summary was updated on November 1, 2004. This summary was updated on January 21, 2005, following the release of a public health advisory from the U.S. Food and Drug Administration regarding the use of nevirapine. This summary was updated on April 12, 2005. An addendum was included on July 18, 2005. This NGC summary was updated on October 10, 2005 and May 10, 2006. This summary was updated by ECRI on July 3, 2006, following the U.S. Food and Drug Administration advisory on Aptivus (tipranavir). This summary was updated on October 12, 2006. This summary was updated by ECRI on April 16, 2007, following the U.S. Food and Drug Administration advisory on Baraclude (entecavir). This summary was updated most recently by ECRI Institute

on May 2, 2007. This summary was updated by ECRI Institute on September 5, 2007, following the revised U.S. Food and Drug Administration advisory on Baraclude (entecavir). This summary was updated by ECRI Institute on October 2, 2007, following the U.S. Food and Drug Administration advisory on Viracept (nelfinavir mesylate).

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Date Modified: 10/22/2007